REMARKS/ARGUMENTS

Claims 1-3, 7, 8, 12 and 13 are pending and previously undergoing examination on the merits. Claims 1, 2 and 12 would be amended herein. Claims 46-50 are newly presented. Claims 9, 10, 24, 25, 27, 29, 30, 33, 37, 38, 44 and 45 were previously canceled. Claims 4 - 6, 11, 14-23, 26, 28, 31, 32, 34-36, and 39-43 stand withdrawn from consideration. After entry of the amendments, claims 1-3, 7, 8, 12, 13 and 46-50 will be pending.

Claim 1 stands rejected under 35 U.SC. §112, first paragraph for an alleged lack of enablement.

Claim 1 stands rejected under 35 U.SC. §112, second paragraph for an alleged lack of written description or indefiniteness.

Claims 1, 3, 7-8, and 12-13 stand rejected under 35 U.S.C. §102(e) as allegedly anticipated by Murphy (U.S. Patent No. 6,022,950).

Claims 1, 3, 7-8, and 12-13 stand rejected under 35 U.S.C. §102(e) as allegedly anticipated by Pastan et al (U.S. Patent No. 6,074,644).

Claims 1, 3, 7-8, and 12-13 stand rejected under 35 U.S.C. §102(e) as allegedly anticipated by Pastan et al (U.S. Patent No. 6,011,002).

Claims 1-3, 7-8, and 12-13 stand rejected under 35 U.S.C. §103/§102(e) as allegedly unpatentable over Wells et al. (U.S. Patent No. 6,498,233) in view of Pastan et al (U.S. Patent No. 6,074,644).

Applicants respond to the above rejections below. Applicants would also like to thank the Examiner for withdrawal of several earlier grounds for rejection.

Support for the Amendments to the Claims

Claim 1 would be amended to recite

> A non-toxic Pseudomonas exotoxin A-like chimeric immunogen comprising in sequence: (1) a cell recognition domain of between 10 and 1500 amino acids that binds to a cell surface receptor of a cell from a mammal; (2) a translocation domain comprising an amino acid sequence at least 90% identical to the

sequence of Pseudomonas exotoxin A (PE) (SEQ ID NO:2) from amino acid position 280 to amino acid position 344 thereof and wherein the domain is capable of effecting translocation to the cytosol of the cell; (3) an epitope presenting domain having one cysteine to cysteine disulfide bonded loop and comprising an amino acid sequence of between 5 and 350 amino acids that encodes an epitope that is non-native to PE domain Ib and is located within the loop, and wherein the epitope is from a pathogen; and (4) an endoplasmic reticulum (ER) retention domain wherein the ER domain is capable of effecting translocation to the endoplasmic reticulum of the cell and wherein the ER retention domain lacks ADP ribosylation activity.

Support for the recited sequence of the domains is found *inter alia* in the specification at p. 23, lines 9-18. Support for the recital of a "cell from a mammal" is found in the specification at p. 22, lines 3 and 4. Support for the translocation domain subject matter is found *inter alia* in the specification at p. 27, lines 1-10. Support for the recital of 90% identity is further found in the specification in the paragraph bridging pages 15 and 16. Support for the endoplasmic reticulum retention domain subject matter which lacks ADP ribosylation activity is found *inter alia* in the specification at p. 31, lines 9-13. Support for the endoplasmic reticulum retention domain subject matter which effects translocation to the endoplasmic reticulum is found in the specification starting at p. 30, second full paragraph.

Claim 2 would be amended to delete an element made redundant in view of the amendments to the base claim.

Claim 12 would be amended for purposes of clarity and to conform with the amendments made to the base claim. Support for such Domain III subject matter is found in the specification *inter alia* at p. 31, second full paragraph.

New claims 46 and 47 set forth subject matter of 95% and 98% sequence identity which is supported in the specification by paragraph 1 on p. 16 and as set forth for claim 1.

New claim 48 depends from claim 15 and sets forth a sequence having 100% identity with respect to the referenced sequence. This subject matter is supported in the specification at p. 27, lines 1-10.

New claim 49 recites depends from claim 1 and sets forth the cell is from a rodent or rabbit. Support for this subject matter is found in the specification *inter alia* at p. 49, line 28-29 (rabbits) and p. 39, last line (rodents).

New claim 50 depends from claim 1 and sets forth the cell is from a primate or human. Support for such is found in the specification *inter alia* at p. 22, lines 3 and 4.

In view of the above, the Applicants believe that the amendments to the claims add no new matter and respectfully request their entry.

Response to the Rejection of Clam for an Alleged Lack of Enablement of the Translocation Domain Subject Matter

Whether undue experimentation[1] is required to practice an invention is typically determined by evaluating: (i) the relative skill of those in the art; (ii) the nature of the invention; (iii) the breadth of the claims; (iv) the amount of guidance presented; (v) the presence of working examples; (vi) the state of the art; (vii) the predictability of the art; and (viii) the quantity of experimentation necessary. *Ex parte Forman*, 230 U.S.P.Q. 546 (PTO Bd. Pat. App. & Inter. 1986), *In re Wands*, 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988). Applicants address each of these factors and the Examiner's concerns as to each in turn.

i. *Relative Skill of those in the Art.*

Applicants submit that the relative skill of those in the art is high.

ii. *Nature of the Invention.*

---

[1] That some experimentation may be necessary to identify operative species does not constitute a lack of enablement. As the Federal Circuit has stated, "the key word is 'undue', not 'experimentation' " in determining whether pending claims are enabled. *In re: Wands*, 8 U.S.P.Q.2d at 1405 (Fed. Cir. 1988). Indeed, a considerable amount of experimentation is permissible if it is merely routine, or if the specification in question provides a reasonable amount of guidance for practicing the invention.

The field of the invention is in the pharmaceutical arts, more particularly vaccine development and antibody production. It is a field in which it is routine to screen a large number of compounds and compositions for their biological activity. It is a field in which the courts have held that the necessary showing for enablement does not require testing in humans. The Applicant need not demonstrate clinical efficacy. See *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995).

iii. Breadth of the Subject Matter at Issue.

Without acquiescing to the position of the Action, and in order to expedite prosecution of the present application, Applicants have amended the base claim to recite:

> a translocation domain comprising an amino acid sequence at least 90% identical to the sequence of Pseudomonas exotoxin A (PE) (SEQ ID NO:2) from amino acid position 280 to amino acid position 344 thereof and wherein the domain is capable of effecting translocation to the cytosol of the cell;

This recital sets forth an amino acid sequence at least 90% identical to that of the portion of the PE domain II which is critical to its translocation activity.

The Action stated that "absent the amino acid sequence comprising a critical amino acid sequence that would evidence translocation activity, the instantly claimed invention is not enabled for the claimed invention." Applicants have adopted the Examiner's suggestion to set forth in the claim the portion of the domain comprising the relevant critical amino acid sequence. Applicants have further amended the claim to set forth an at least 90% sequence identity.

Applicants further call the Examiner's attention to dependent claims 2 and 14-16 which set forth subject matter having 95%, 98% or complete sequence identity with the specified translocation sequence of PE.

iv. Amount of Guidance Presented.

Applicants describe the portions of Domain II that are important to the translocation capability on p. 27, first two full paragraphs. These paragraphs further indicate critical amino acids which are essential to activity in Domain II.

The specification further teaches all the methods required to practice the subject matter at issue. The Action discloses that methods for testing the ability of a chimeric immunogen to translocate to the cytosol are the subject of routine assays. These methods are generally described on p. 32 and are further exemplified on p. 49, first three full paragraphs.

v. Presence of Working Examples.

The specification provides a working example of a nontoxic PE-like chimera according to the base claim (see Ex. 1 on p. 45 and see also p. 52, lines 15-24). This chimera comprises a modified PE protein which has a PE domain Ia, a PE domain Ib modified to accommodate an epitope from the pathogen HIV between a cysteine-cysteine loop, a PE domain II comprising the critical sequence of PE domain II, and a PE domain III which has been modified to eliminate the ADP ribosylation capability,

vi. State of the Art.

The state of the art is high and particularly advanced in the subfield involving re-engineered PE. As discussed in Murphy, EP 0349954 A2 (1990) at p. 5, lines 34-40 (already of record), the translocation domains of PE are well characterized. Indeed, there is much art in the literature devoted to PE chimera. Such art includes many other Pastan et al. patents cited in the Information Disclosure Statements as well as the references cited in the present Action. In particular, Applicants refer the Examiner to Kuan et al. J. Biol. Chem. 7610-7616 (1994) (already of record) which discloses various modifications to PE domain II (*see*, in particular, the first paragraph of p.112 thereof).

(vii) Predictability of the Art.

The art is predictable. The above references illustrate that domain II variants retaining their translocation capabilities can be readily obtained.

viii. Quantity of Experimentation Necessary.

The field of the invention is the pharmaceutical arts. A great deal of experimentation is quite routine in this field. It is a field which is largely devoted to the screening and testing of a large number of candidate compounds, compositions and treatments in model systems[2]. In addition, as noted above, the Courts do not require clinical testing to demonstrate utility.

The subject matter of PE domain II variants which can retain their translocation function is well set forth in the specification as well as the art of record. Thus, relatively little additional experimentation would be required to practice other such embodiments of the invention.

Overall Summary of the Wands Analysis

Here,

(i) the relative skill and experience of those in the art of vaccine development is generally quite high;

(ii) the nature of the invention involves testing PE chimera in model test systems which are well known in the art.

(iii) the breadth of the claims is completely commensurate with the specification disclosure;

---

[2] Indeed, The Federal Circuit has held that if a specification teaches one embodiment and sets forth a method for determining dose/response, the experimentation required to determine a dose/response curve is not undue, even if the studies proved to cost approximately $50,000 and took 6-12 months to accomplish. *United States v. Telectronics,* 8 USPQ2d 1217 (Fed. Cir. 1988)(enclosed).

(iv) the specification provides adequate guidance for all manipulations required to practice the invention;

(v) the specification provides working examples;

(vi) the state of the art is high, involving modifications to a toxin (i.e., PE) that is very well-known;

(vii) noting that FDA standards as to operability are not those set forth for patentability, the art is sufficiently predictable such that one of ordinary skill in the art would consider the disclosed data to support the operability of the claimed subject matter;

(viii) while the field of art is one in which a great deal of experimentation is routinely performed by a person of ordinary skill in the art, in fact, relatively little additional research would be required to practice the invention.

In view of the above, Applicants believe that one of ordinary skill in the art could readily practice the invention as claimed using an amount of experimentation which would be clearly routine in the art. Applicants therefore request that the above rejection be reconsidered and withdrawn.

B. Rejection targeting the recital of ("PE-like").

Without acquiescing to the position of the Action, and in order to expedite prosecution of the present application, Applicants have amended the base claim to delete the offending recital.

In view of the above, Applicants respectfully request that the above rejection be reconsidered and withdrawn.

C. Rejection targeting the recital of "capable of effecting translocation into the cytosol."

Without acquiescing to the position of the Action, and in order to expedite prosecution of the present application, Applicants have amended the base claim, as suggested by the Examiner, to set forth subject matter more clearly drawn to the critical portion of Domain II. Further, the base claim has been amended to set forth that the cell is a cell from a mammal.

Applicants note in accord with each of the references cited in the instant Action, that the specificity of the chimeric molecules is with respect to the cell recognition domain and that the translocation domains operate upon a diversity of cell types targeted by the cell recognition domain. For instance, the PE constructs for Wels (U.S. Patent No. 6,498,233) and Pastan et al. (U.S. Patent No. 6,011,002 and U.S. Patent No. 6,074,644) each target a diversity of cell types using different cell recognition domains without varying the translocation domain according to cell type. The specification illustrates the PE II domain translocation sequence operates in rabbits (p. 49, line 26-30), mice (p. 53, line 22, and human cell lines ((Caco-2 cells; see p.52, lines 28-31), (human epithelial cell line A431; see, p. 49, line 14))

In view of the above, Applicants respectfully request that the above rejection be reconsidered and withdrawn.

D. Rejection targeting the recital "an epitope presenting domain located at the PE 1b domain location."

Without acquiescing to the position of the Action, and in order to expedite prosecution of the present application, the base claim has been amended to delete the recital of "an epitope presenting domain located at the PE 1b domain location."

Applicants have further amended the claim to recite "comprising in sequence" and to list such domains thereafter in the sequence as set forth in the first paragraph of p. 23.

In view of the above, Applicants respectfully request that the above rejection be reconsidered and withdrawn.

E. Rejection targeting the subject matter of "a non-toxic *Pseudomonas* exotoxin A-like ("PE-like") chimeric immunogen."

To answer the Action's questions, the chimeric immunogen is like non-toxic *Pseudomonas* exotoxin A in having receptor binding, translocation, and endoplasmic reticulum retention functional domains and having these functional domains in essentially the same sequence as that of *Pseudomonas* exotoxin A. This sequence is in accord with the sequence set

forth in the first paragraph of p. 23. The immunogen is further like *Pseudomonas* exotoxin A in having a domain located between the translocation and endoplasmic reticulum domains that comprises a cysteine to cysteine bonded loop. The immunogen is further like non-toxic *Pseudomonas* exotoxin A in comprising an amino acid sequence identical to a portion of the amino acid sequence of a portion of the translocation domain of *Pseudomonas* exotoxin A conferring translocation activity. The immunogen is further like non-toxic *Pseudomonas* exotoxin A in comprising an endoplasmic reticulum retention sequence lacking ADP ribosylation activity.

In view of the above, Applicants respectfully request that the above rejection be reconsidered and withdrawn.

Response to the Rejections for an Alleged Lack of Novelty Under 35 U.S.C. §102.

In accord with MPEP §2131 ("to anticipate a claim the reference must teach every element of the claim.") Applicants respectfully respond to the several anticipation rejections below.

A. Alleged Anticipation by Murphy (U.S. Patent No. 6,022,950).

As a threshold matter, Applicants would like to point out that Murphy discloses a three-part hybrid molecule comprising a first part comprising a cell recognition portion, a second part comprising a translocation portion, and a third part comprising a chemical entity to be introduced into the subject cell.

1) Murphy simply does not disclose the subject matter of

> an endoplasmic reticulum (ER) retention domain wherein the ER domain is capable of effecting translocation to the endoplasmic reticulum of the cell and wherein the ER retention domain lacks ADP ribosylation activity.

2) Nor, did Murphy disclose locating his third part chemical entity between an ER retention domain and the translocation domain.

3) Whenever Murphy did disclose the use of a *Pseudomonas* exotoxin A translocation domain sequence, Murphy specifically excluded the 'third part' of their chimera from being a polypeptide (see base claim 1, see Abstract, see Summary). Where Murphy recites in claim 19 the use of an enzymatically active portion of a *toxin* and further recites in claim 26, which depends from claim 19, a list of bacterial toxins including that of *Pseudomonas* exotoxin A, Murphy is describing *toxic* subject matter which is specifically excluded from the instant claims which recite a *non-toxic Pseudomonas* exotoxinA-like immunogen and set forth that the endoplasmic reticulum retention sequence lacks ADP-ribosylation activity (to render it non-toxic).

Moreover, claim 19 of Murphy depends from claim 4 which recites that the third part is a polypeptide. And claim 4 in turn depends from claim 1, and claim 1 specifically recites that when the second part comprises a portion of a translocation domain of *Pseudomonas* exotoxin A, the third part is not a polypeptide. Thus, claims 4, 19, 22 and 26 of the Murphy patent exclude the subject matter wherein the translocation domain comprises a translocation sequence of *Pseudomonas* exotoxin A.

The subject matter of claim 43, which depends from claim 34, is drawn to a hybrid molecule having a translocation domain of diphtheria toxin, not *Pseudomonas* exotoxin A.

In view of the above, Applicants request that the above rejection be reconsidered and withdrawn.

B. Alleged Anticipation by Pastan et al. (U.S. Patent No. 6,074,644).

Generally, the '644 Pastan et al. patent primarily discloses *toxic* immunotoxins. generally comprising an antibody or antibody fragment. The instant claims are directed toward *non-toxic* immunogens which in some aspects of the invention can be used to produce antibodies.

The instant base claim recites "an epitope that is non-native to PE domain Ib and is located within the loop, and wherein the epitope is from a pathogen." Assuming for the sake

of argument that the placement of the antibody of the '644 Pastan et al. patent is at the Ib position, such disclosure does not disclose placing "epitopes from a pathogen" there.

As the '644 Pastan et al. patent does not disclose each and every element of the base claim, this reference can not anticipate the claimed invention. Applicants therefore respectfully request that the above rejection be reconsidered and withdrawn.

C. Alleged Anticipation by Pastan et al. (U.S. Patent No. 6,011,002)

With respect to compositions, generally, the '002 Pastan et al. patent primarily concerns circularly permuted ligands and chimeric molecules comprising them. Ligand is defined in the '002 Pastan et al. patent thusly:

> A "ligand", as used herein, refers generally to all molecules capable of reacting with or otherwise recognizing or binding to a receptor, antigen, or other molecule on a target cell. Specifically, examples of ligands include, but are not limited to antibodies, lymphokines, cytokines, receptor proteins such as CD4 and CD8, solubilized receptor proteins such as soluble CD4, hormones, growth factors, and the like which specifically bind desired target cells.

('002 Pastan et al. patent at Col, 8, lines 39-46).

The instant base claim recites " an epitope that is non-native to PE domain Ib and is located within the loop, and wherein the epitope is from a pathogen." Assuming for the sake of argument that the placement of the circularly permuted ligand of the '002 Pastan et al. patent is at the Ib position, the *species* of circularly permuted ligands wherein the ligand comprises an "an epitope that is non-native to PE domain Ib and is located within the loop, and wherein the epitope is from a pathogen" does not appear to be disclosed anywhere in the '002 Pastan et al. patent.

The Action cited Col. 17 lines 7-15 as setting forth subject matter wherein a circularly permuted ligand is fused to PE. The paragraph recites:

> Where the circularly permuted ligand is fused to PE, i preferred PE molecule is one in which domain Ia (amino acids 1 through 252) is deleted and amino acids 365 to 380 have been deleted from domain lb. However all of domain Ib and a portion of domain II (amino acids 350 to 394) can be deleted,

> particularly if the deleted sequences are replaced with a linking peptide such as GGGGS (SEQ ID NO:54).

However, this paragraph does not disclose a circularly permuted ligand located at the Ib position. It suggests no particular utility for the Ib site.

Next, the Action cites col. 17, lines 19 - 24 as disclosing chimeric protein having the circular permutation at the Ib position. However, the specification recites therein that

> The circularly permuted ligand may also be inserted at a point within domain III of the PE molecule. Most preferably the circularly permuted ligand is fused between about amino acid positions 607 and 609 of the PE molecule. This means that the circularly permuted ligand is inserted after about amino acid 607 of the molecule and an appropriate carboxyl end of PE is recreated by placing amino acids about 604-613 of PE after the circularly permuted ligand. Thus, the circularly permuted ligand is inserted within the recombinant PE molecule after about amino acid 607 and is followed by amino acids 604-613 of domain III. The circularly permuted ligand may also be inserted into domain Ib to replace sequences not necessary for toxicity. Debinski, et al. Mol. Cell. Biol., 11: 1751-1753 (1991).

The above paragraph cited by the Action clearly recites that the circularly permutated ligand may be inserted at position Ib to avoid replacing sequences *not necessary for toxicity*. Thus, the reference suggests to place the circularly permutated ligand at the Ib position to preserve toxicity. In contrast, the instant claims concern a *non-toxic* chimeric immunogen to which the recital simply does not apply.

The Action incorrectly cites col. 17 lines 38-51 of the '002 Pastan patent as also disclosing a generally *non-toxic* chimera. This portion of the Pastan reference recites:

> Those skilled in the art will realize that additional modifications, deletions, insertions and the like may be made to the circularly permuted ligand and PE genes. Especially, deletions or changes may be made in PE or in a linker connecting an antibody gene to PE, in order to increase cytotoxicity of the fusion protein toward target cells or to decrease nonspecific cytotoxicity toward cells without antigen for the antibody. All such constructions may be made by methods of genetic engineering well known to those skilled in the art (see, generally, Sambrook et al., supra) and may produce proteins that have differing properties of affinity, specificity, stability and toxicity that make them particularly suitable for various clinical or biological applications.

However, the rationale for the combination of the PE toxin with the circularly permuted ligand is set forth at col. 15, lines 44-59 thusly:

> Chimeric ligand-toxin molecules are of particular interest and comprise a circularly permuted ligand joined to a toxin. Particularly preferred are chimeric toxin fusion proteins. One of skill in the art would recognize that many toxins are suitable including Pseudomonas exotoxin, Diphtheria toxin, other bacterial toxins, and derivatives of plant or animal toxins. In a preferred embodiment, the fusion protein comprises a circularly permuted growth-factor fused to either a Pseudomonas exotoxin or a Diphtheria toxin.
>
> Pseudomonas exotoxin A (PE) is an extremely active monomeric protein (molecular weight 66 kD), secreted by Pseudomonas aeruginosa, which inhibits protein synthesis in eukaryotic cells through the inactivation of elongation factor 2 (EF-2) by catalyzing its ADP-ribosylation (catalyzing the transfer of the ADP ribosyl moiety of oxidized NAD onto EF-2).

The specification clearly sets forth that the combination of a circularly permuted ligand with PE exotoxin is meant to produce an agent with enhanced toxicity for target cells. Thus, it is not reasonable to conclude that the passage cited by the Examiner suggests a modification to eliminate toxicity for the *target* cell by eliminating the ADP-ribosylation activity of PE exotoxin portion of the chimeric molecule. In fact, the passage is fairly construed as generally setting forth a more *selectively* toxic chimeric toxin rather than a non-toxic chimeric toxin as proposed by the Action.

Most importantly, the circularly permuted ligands function are primarily disclosed as cell recognition domains. For instance, see the Summary which sets forth at col. 2, lines 19-46:

> The circularly permuted ligands are especially useful when employed as a component in a chimeric molecule such as a fusion protein of interest. Oftentimes fusion, or chemical conjugation, of a protein to an original terminus of a ligand interferes with binding of the ligand to its native receptor. For example, fusing a toxin to the carboxy terminus of IL4 greatly interferes with the binding of IL4 to its receptor.
>
> Specific binding affinity of IL4-containing chimeric molecules (e.g. fusion proteins) and cytotoxicity of toxin fusion proteins is greatly enhanced by the use of the circularly permuted (CP) ligands (e.g. CP IL4) described herein. The

> increased affinity and cytotoxicity obtained by circular permutation of the targeting molecule renders the chimeric CP ligand-cytotoxin molecules of the present invention particularly well suited for in vivo use. Thus this invention provides for methods of inhibiting the in vivo growth of tumor cells by contacting the cells with the cytotoxic chimeric molecules, in particular cytotoxic fusion proteins described herein. In addition, this invention provides for a method of specifically delivering a molecule (e.g., an effector molecule such as a cytotoxin, an antibody, a ligand, a drug, a liposome, a label, a binding protein, a radioactive compound, etc.) to a target cell in vivo. The method involves administering to a mammal a molecule comprising a circularly permuted ligand in a pharmaceutically acceptable carrier; wherein the ligand specifically binds the target cell.

Thus, even if assuming for the sake of argument that the circularly permuted ligand is located at the Ib position and that such disclosure would be relevant to a non-toxic chimera, the circularly permuted ligand is functioning as the cell recognition domain. The present claims recite a chimeric immunogen having, in sequence, a cell recognition domain, a translocation domain, the epitope domain and the endoplasmic reticulum domain. It does not recite the sequence of a translocation domain, a cell recognition domain, and an endoplasmic reticulum domain.

In view of the above, Applicants respectfully request that the above rejection be reconsidered and withdrawn.

Response to the Rejection for Alleged Unpatentability over Wels et al. (U.S. Patent No. 6,498,233) in view of Pastan et al. (U.S. Patent No. 6,074,644).

As a threshold matter, Applicants would like to note that MPEP §2143 sets forth the basic requirements of a *prima facie* case of obviousness thusly:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

A proper obviousness rejection requires, *inter alia*, that the prior art 1) suggest making the claimed invention and 2) provide a reasonable expectation of successfully practicing the claimed invention. Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in Applicant's disclosure. MPEP § 2143; *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991).

A. The suggestion to combine the references is <u>not</u> found in the cited art.

The Action alleges that claim 1 of the Wels patent discloses "a nucleic acid binding *protein*" domain [italics added for emphasis]. Actually, the Wels base claim recites

> 1. A multidomain protein comprising, a target cell-specific binding domain, a translocation domain and a nucleic acid binding domain, wherein the translocation domain is derived from a diphtheria toxin but does not include the cytotoxic part of said diphtheria toxin, wherein the translocation domain is derived from amino acids 194-378 or 196-384 of said diphtheria toxin.

The Wels specification leaves no doubt that the nucleic acid binding domain of Wels is <u>not</u> a nucleic acid binding *protein*. In fact, the title of the Wels patent recites "Nucleic Acid Transfer System" and the specification is in accord with this assertion. See, for instance, col. 1 (lines 51-65) of the Wels specification which recites:

> Thus there is still a need for a simple, efficient nucleic acid transfer system which allows e.g. the target cell-specific introduction of nucleic acids to be expressed, but lacks the disadvantages of the prior art concepts.
>
> It is the object of the present invention to provide such a system. The nucleic acid transfer system according to the invention is characterized by the following two components:
>
> 1) a multi-domain protein comprising several functional domains including a nucleic acid binding domain
>
> 2) an effector nucleic acid, particularly a DNA, comprising the nucleic acid, e.g. the gene, to be delivered to and expressed in a selected target cell, and a cognate structure recognizable by the nucleic acid binding domain of the protein.

Assuming that Wels discloses placing a moiety at the Ib position of PE exotoxin, Wels puts a nucleic acid there, not a protein.

The Examiner cites the '644 Pastan et al. patent as disclosing "a disulfide stabilized binding agent." The subject "disulfide stabilized binding agent" generally comprises antibody V_H and V_L fragments and similar constructs (see col. 7, lines 1-5, and lines 21-35). The '644 specification defines "binding agents" at col. 11,lines 9-16, thusly:

> The "binding agents" referred to here are those molecules that have a variable domain that is capable of functioning to bind specifically or otherwise recognize a particular ligand or antigen. Moieties of particular interest include antibodies and T cell receptors, as well as synthetic or recombinant binding fragments of those such as Fv, Fab, F(ab').sub.2 and the like. Appropriate variable regions include V.sub.H, V.sub.L, V.sub..alpha., and V.sub..beta. and the like.

These fragments may be linked, as in the natural antibodies, by disulfide bridges between cysteine residues. The existence of such disulfide bridges is simply not relevant to nucleic acids which do not have cysteine as chain residues which need to be linked for functionality. The proffered motivation for their combination simply fails to apply to the combination.

B. The proposed combination does not satisfy all the elements of the claims.

As noted above, generally, the '644 Pastan et al. patent primarily discloses *toxic* immunotoxins generally comprising an antibody or antibody fragment. The present claims are directed toward *non-toxic* immunogens which, in some aspects of the invention, can be used to produce antibodies.

The instant base claim recites " an epitope presenting domain having one cysteine to cysteine disulfide bonded loop and *comprising an amino acid sequence* of between 5 and 350 amino acids that encodes an epitope that is non-native to PE domain Ib and is located within the loop, and wherein the epitope is from a pathogen." As noted above, assuming for the sake of argument that the Wels *nucleic acid* were to be substituted for the antibody fragments of the '644 patent, the combination would not provide "an epitope presenting domain having one cysteine to

cysteine disulfide bonded loop and *comprising an amino acid sequence* of between 5 and 350 amino acids."

In view of the above, Applicants respectfully request that the above rejection be reconsidered and withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe they have complied with the requirements of the Notice of Non-Compliant Amendment (37 CFR 1.121) mailed March 11, 2004 by providing a complete listing of all of the claims and presenting the claims in ascending numerical order.

Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If it is believed that a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,

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Attachments

FJM:fjm
60166254 v1